AREA OF EMPHASIS:

Vaccines

SCIENTIFIC ISSUES

Prophylactic HIV vaccines might prevent and/or control HIV infections in several ways: by completely preventing HIV infection, by controlling the level of virus and preventing the development of AIDS, or by preventing HIV transmission from vaccinated individuals. As we seek multiple strategies to bring the global AIDS pandemic under control, HIV vaccine research continues to be a top priority for the NIH. Over the past 9 years, the NIH has increased support for a broad program encompassing basic, preclinical, and clinical research on HIV/AIDS vaccines to its current level at more than five times the budget allocated in FY 1996. The first efficacy trials of candidate vaccines composed of bivalent, recombinant gp120 envelope proteins with alum adjuvant were completed in North America and in Thailand in 2002–2003 by VaxGen. These trials of candidate vaccines, which relied on the ability to induce neutralizing antibody to HIV, failed to provide evidence of protection against HIV infection or disease. This failure appears to be related to the limited breadth of the virus neutralization response induced by these and other monomeric gp120 vaccines and the limited cellular immune responses induced by recombinant proteins. Additional analyses of trial data and samples from these and related clinical trials may provide clues to guide future vaccine designs. Vaccine candidates inducing primarily cellular immune responses advanced to large efficacy or proof-of-concept, efficacy trials in 2003 and 2004. These trials utilize vectors that produce several HIV proteins but do not replicate in human cells—either a nonreplicating poxvirus vector (canary pox) or nonreplicating adenovirus vector (Ad 5). These vectors, by design, are very safe strategies to provide HIV antigens to stimulate the immune system. These trials will test whether vaccine-induced

cellular immune responses, measured in peripheral blood, will be sufficient to reduce HIV infection or control of viral load in vaccinated individuals. As a result of increased funding from the NIH in the area of basic HIV/AIDS vaccine research, many new approaches to HIV vaccines are being studied in preclinical testing in animal models. Novel and improved HIV vaccine candidates are being rapidly developed for clinical use. During the next 2 years, 6 to 10 additional products or combinations of current candidate vaccine products are expected to enter Phase I and/or Phase II safety and immunogenicity trials in human volunteers, reaching decision points for proof-of-concept, efficacy trials within 3 to 4 years. With the number of trials already ongoing, this will put a strain on the existing network of domestic and international sites currently conducting trials. As promising candidates move further in the HIV vaccine pipeline, it will become increasingly important to expand the trained core of personnel who are able to recruit volunteers and conduct HIV vaccine trials. Interested and committed individuals in their communities will become key players in the HIV vaccine effort as they inform and counsel individuals at increased risk for HIV infection about prevention of HIV infection. Fortunately, more organizations and companies are involved in HIV vaccines than ever before, and issues of coordination and cooperation have become an important component of the HIV vaccine agenda. The cross-agency Partnerships for AIDS Vaccine Evaluation (PAVE), involving key U.S. Government agencies conducting HIV vaccine trials, led by the National Institute of Allergy and Infectious Diseases (NIAID), has developed timely initiatives for harmonization and coordination of selected aspects of HIV vaccine trials and their evaluation. This has led to close collaborations between Government-sponsored trial sites and other networks and effected early implementation of some of the goals of the Global HIV/AIDS Vaccine Enterprise (GHAVE). In 2005 the NIH will fund the first of the vaccine centers imagined in the GHAVE plan. The Center for HIV/AIDS Vaccine Immunology (CHAVI) will focus intense collaborative research efforts on dissecting and defining potential correlates of immune protection.

Vaccine Design

Basic research on the virus and on the human immune responses to HIV infection continues to provide the crucial foundation for the design and development of novel AIDS vaccine candidates. Building on the insights of recent basic research findings on the structural components of HIV, particularly those related to the HIV envelope, and studies on immune responses in small animals and nonhuman primates (NHPs), new vaccine candidates are being designed and tested. One of the major hurdles that still complicates HIV vaccine design is the wide genetic diversity of HIV, particularly in the HIV envelope. At the same time, HIV is constrained to enter cells through specific coreceptors and to replicate in a host. To address HIV diversity, vaccine candidates are being constructed based on isolates from many regions of the world, and several research groups are exploring combinations of viral

envelopes from different isolates and/or clades. Natural HIV variants that express conserved envelope epitopes for neutralization seen on a wide range of strains are being sought. In addition, concepts that generate genetic copies of HIV that represent either a consensus of the genetic sequences for some HIV subtypes or ancestral HIV for the main, M group of HIV-1 strains are being explored. Investigators also are testing HIV vaccine candidates that express conformationally appropriate trimeric envelope structures. Initial reports suggest that trimeric envelope proteins or virus-like particles that display envelope trimers provide an incremental step to improved neutralizing antibodies against a panel of HIV isolates. Others are seeking to identify or develop HIV envelope structures or mimics which either present selected critical epitopes or are more broadly immunogenic than recombinant envelope gp120 proteins that have been tested in clinical trials. Envelope proteins of viruses isolated from individuals newly infected with clade C or A may have shorter variable loops and reduced glycosylation, suggesting that envelopes of transmitted viruses may provide a base for novel vaccine designs. Recent data from human and NHP acute infection studies confirm the profound early loss of memory CD4 T cells in mucosal tissues, intensifying the need for studies of vaccines inducing mucosal immunity. Information about the processing of HIV gag structural components offers new ways to inactivate the virus and add safety features to HIV vaccine constructs. Several vaccine strategies are exploring adjuvants, immune modulators, and improved delivery components to optimize the immune responses that are generated by various HIV vaccine candidates. Basic studies on the mechanisms of antigen presentation, rules of engagement of both innate and adaptive immune responses, and vaccine designs to engage the most effective antigen presentation are ongoing. Finally, safety studies of improved constructs have addressed some of the concerns about replicating vectors which appear to provide higher initial immune stimulation.

Animal Model Development and Testing of Vaccines

Suitable animal models, especially NHPs, are crucial for further development and preclinical testing of new HIV/AIDS vaccine candidates. The NIH continues to support the expansion of macaque colonies and the development of appropriate biosafety housing to ensure resources for proof-of-concept studies for HIV vaccines as well as other important pathogenesis and microbicide research. Because HIV does not replicate in monkeys without adaptation, simian immunodeficiency viruses (SIV) or recombinant chimeric simian-human immunodeficiency viruses (SHIV) have been used. However, pathogenicity and vaccine studies with SHIVs have revealed a number of limitations. The highly pathogenic recombinant SHIVs (e.g., SHIV 89.6P), even those with dual tropic envelope, utilize the CXCR4 coreceptor and do not recapitulate the slow, progressive, pathogenic loss of peripheral blood CD4 T cells seen in HIV-infected persons. It also appears easy for HIV envelope vaccines to induce protection from disease progression with even a modest impact on the initial viral replication of SHIV strains or with low levels of neutralizing antibody to the virus. Unfortunately, the SIVs, which more closely mimic HIV

disease progression, do not permit direct evaluation of candidate HIV vaccines that incorporate HIV envelope components. Recent observations of genetic polymorphisms of TRIM 5 alpha genes in macaques may explain some of the variation in replication of SIV stocks previously observed *in vivo*. SF162 SHIV stocks, which use an envelope gene from a macrophage-tropic HIV isolate, using CCR5 chemokine receptors, are now being studied extensively in macaques. In addition, SHIV strains that reflect the kinds of viral diversity seen in the global epidemic are being constructed and tested to prepare viruses for testing of vaccine strategies that incorporate diverse HIV envelope components. Several groups have been developing animal models to address questions of repeated low-dose vaginal or rectal mucosal exposure and oral mother-to-child transmission (MTCT) of HIV. The latter may serve both as models for passive immunity to address neonatal transmission and as infant models to address questions of vaccine-induced prevention of breastfeeding transmission.

Correlates of Immune Protection

There is, as yet, no single correlate of immune protection that can be used as a yardstick to compare the kinds of protection observed in different animal models. However, AIDS vaccine candidates with at least limited protection using monkey models have provided strong scientific rationales to further explore and develop several vaccine concepts and to move additional vaccine candidates into clinical testing. Evidence is accumulating from HIV/AIDS vaccine research that the correlate of protection will be some complex of both cellular and humoral immunity that may not be measured by assays currently employed. The CHAVI cooperative agreement will be a key component of the NIH portfolio that will investigate correlates of immune protection. In parallel, additional basic research is needed to better understand what makes some individuals either resistant to infection when they are exposed to HIV or able to control the infection so that disease progression is slowed even without the use of antiretroviral therapy (ART). Recent information about viral escape from neutralizing antibodies in both adults and infants suggests that these antibodies can be an important correlate of immunity. Other data suggest that neutralization of HIV is not the only function of antibodies that may be employed *in vivo*, where antibody-dependent, cell-mediated cytolysis may be triggered. Further, studies of virus envelope sites recognized by antibodies from infected persons indicate that the human immune system effectively recognizes epitopes induced by virus attachment to CD4, CD4i epitopes, which are shared across a wide range of HIV-1 and HIV-2 isolates. While some individuals with specific major histocompatibility genotypes are able to mount strong protective cellular immune responses, it is not clear whether vaccine candidates can similarly induce and maintain these kinds of responses in the broader population at risk of infection. Also it is not clear which components of these immune responses are necessary and sufficient for protection. This poses a need to move more complex

candidate vaccines and combinations of vaccines into human clinical trials and to develop novel assays to obtain some of these answers.

Clinical Trials and Site Development

Over the past 7 years, the HIV Vaccine Trials Network (HVTN) has expanded from a small number of domestic sites conducting Phase I and II vaccine trials that were present in the AIDS Vaccine Evaluation Group (AVEG) to a network, now consisting of 16 domestic and 15 international sites for the conduct of Phase I, II, and III clinical trials. Significant efforts are underway to identify and develop access to additional populations necessary to conduct large-scale clinical studies at these and additional sites. In some cases, these sites require substantial infrastructure development and capacity building to ensure that the local clinical researchers, scientists, and medical personnel are appropriately trained to design, conduct, and analyze the clinical trials as full and equal partners. In addition, the active education and full participation of the affected community in these efforts also is critical and must be built in parallel. The HVTN as well as other HIV clinical trial networks will be recompeted in FY 2006 with an effort to consolidate and streamline both the leadership groups and the sites that will conduct prevention and therapeutic clinical trials.

The NIH has now initiated or conducted, in collaboration with academic researchers, government partners, and industry cosponsorship, more than 75 Phase I and 4 Phase II clinical trials of more than 35 vaccine products, individually or in combination, in human volunteers. More than 10 new candidate vaccines have entered clinical trials sponsored by the NIH in the past 18 months, and 6 to 8 additional new products will enter Phase I trials during the next 18 months. Several new combinations of products, which are expected to provide better immune responses in combination than as single immunogens, will also be tested in Phase I or II trials. The Dale and Betty Bumpers Vaccine Research Center (VRC) at the NIH is evaluating the immune responses from its initial clinical trials of multiclade, multigene DNA vaccine candidates boosted with adenovirus vectors with matched inserts. Based on the immune responses observed, these vaccine candidates have been advanced to testing in international sites with PAVE partners including the HVTN, the U.S. Department of Defense U.S. Military HIV Research Program (USMHRP), and the International AIDS Vaccine Initiative (IAVI). The NIH currently is sponsoring Phase I and II HIV vaccine trials of other products in Africa, the Caribbean, South America, and Australia as well as in many sites in the United States. Other international sites are conducting studies to determine seroincidence to assess the feasibility of trials in selected populations. In partnership with the Government of Thailand and the USMHRP, the NIH is supporting a large communitywide Phase III trial of the "prime-boost" concept, utilizing an avipox recombinant vector (ALVAC - vCP1521) to prime the T-cell components

of the immune response to several HIV proteins and a bivalent B/E recombinant gp120 envelope protein product (AIDSVAX B/E) to boost immune responses to the envelope. Enrollment for this trial should be completed before the end of 2005, but study results will not be available until the end of 2008 or early 2009. A large Phase IIb, proof-of-concept, efficacy trial was started in collaboration with Merck in 2004 that will test several aspects of the ability of the 3 gene (gag, pol, and nef) MRKAd5 vaccine candidate to protect from infection or disease progression. Since this vaccine candidate does not include envelope genes, it is more likely that the vaccine will have an effect on viral load and disease progression.

These first proof-of-concept, efficacy trials of the second-generation vaccines are focused primarily on induction of cellular immune responses to control viral load and disease progression with limited breadth of antibody protection against genetically diverse infections. Therefore, the NIH will continue to place a high priority on the development and testing of AIDS vaccine candidates incorporating strategies to induce antibodies to envelope and will provide support for the basic research and preclinical testing needed to continue to resolve this gap in the AIDS vaccine pipeline.

FY 2007 PRIORITIES FOR HIV/AIDS VACCINES

Several priority areas previously identified in the *Fiscal Year 2006 NIH Plan for HIV-Related Research* have been revised and modified to identify the most critical needs to be addressed with limited budget.

PRIORITY FOR FUTURE RESEARCH:

- **Continue to support a broad NIH vaccine research portfolio to ensure a vigorous program of basic and preclinical research for:**
  - **Innovative immunogen design, discovery, preclinical evaluation, and introduction of improved vaccine candidates and immunization concepts. A vigorous pipeline of novel candidates remains a key overarching priority that needs to be balanced with the urgency to develop and test existing HIV vaccine candidates in domestic and international cohorts.**

    The failure of bivalent monomeric recombinant HIV gp120 immunogens to induce responses able to prevent infections in Phase III trials calls for continued emphasis on novel approaches to induce protective antibody responses to HIV envelope. Current candidate HIV vaccine products in development or early testing may provide incremental progress toward this elusive goal. However, further exploration of innovative approaches is still needed to induce high-titered neutralizing antibody responses that are broadly cross-reactive with diverse HIV clades and circulating recombinant forms of HIV.

- **Detailed analyses of the immune responses generated by vaccine candidates that lead to protective immunity.**

HIV vaccine candidates based on strategies to induce strong cellular immune responses, now in or approaching clinical trials, are unlikely to achieve the goal of preventing HIV infection since cellular effector immune responses are directed primarily against infected cells. However, preclinical data from several studies in macaques suggest that control of viral load and delay of disease progression may be achieved if appropriate cellular immunity can be induced against viral antigens. A proof-of-concept trial to evaluate efficacy of a candidate HIV vaccine, focused on induction of cellular immunity, has been initiated. However, urgency exists to develop additional, more highly immunogenic vaccine designs—for example, designs incorporating adjuvants or vectors that deliver persisting antigen or high doses of antigen at the initial immunization—to both prevent HIV infection and provide strong, durable cellular immunity. Support for studies to understand the mechanisms that HIV vaccine candidates use to induce long-lasting memory responses should be encouraged through continuing support for investigator-initiated programs.

PRIORITY FOR FUTURE RESEARCH:

- **Support research on the identification of correlates of immune protection: study the development and maintenance of effective immune responses to HIV antigens, particularly those able to provide protection at mucosal surfaces, address issues related to improvement in the duration of potentially protective immune responses, and develop shared resources for comparative analysis of vaccine candidates.**

It is critically important to continue to investigate host immune responses to determine how they control HIV infection. These studies need to be comprehensive and innovative and should be focused on strategies that induce long-lasting, vaccine-induced immune responses that impair the ability of HIV to establish infection at the sites of transmission or that impair viral replication and dissemination. Several scenarios now have been reported with vaccination or drug-controlled virus exposure in animal models where several previously proposed correlates of immunity (cytotoxic T lymphocytes [CTLs], interferon gamma-producing cells, or neutralizing antibodies) have not been observed. Current candidate HIV vaccine products in preclinical development and in clinical trials may provide some additional information on these kinds of novel protective responses and the means to measure them. Although a comprehensive, concerted effort to identify correlates of immune protection is expected to be funded as the CHAVI in FY 2005, investigator-initiated research to identify key components of a protective immune response and developing the means to optimally measure relevant immune responses between different groups of investigators should remain high priorities for the NIH.

PRIORITY FOR FUTURE RESEARCH:

- **Using the most efficient and cost-effective designs, conduct clinical trials of HIV vaccine candidates in appropriate human populations. If possible, implement direct "head-to-head" comparative studies of vaccine candidates, but the main effort should be directed to the comparative assessment of immune responses with validated assays and standardized methods for sample handling in both preclinical and clinical evaluation of HIV vaccine candidates to enable comparisons across trials. Appropriate reagents, quality assurance assays, and animal models should be developed. Information, standard operating procedures, and reagents should be shared widely to facilitate comparative vaccine studies. To ensure comparability, expanded assessments of cellular immunity and neutralizing antibodies in central laboratories using validated assays and broader access to specimens are encouraged for both academic and industrial investigators.**

Data from several animal models, where protection either has been achieved or has failed, indicate that current assays for vaccine-induced CTLs or antigen-specific gamma interferon induction by CD8+ T cells are not predictive of protection from either infection or immunodeficiency disease endpoints. The urgent need to develop improved or alternative chimeric SIV/HIV/SHIV models that more closely mimic human HIV infection has been recognized, and the NIH should support efforts to generate additional viral stocks and make them widely available as soon as possible. Concerns about the development of an array of similar or related vaccine candidates with little or no comparative data among products often leave the NIH with a limited basis on which to select and move one or more products forward in clinical testing. Tests for neutralizing antibodies often are analyzed with only a few clinical isolates that are available to an individual investigator or company. NHP studies are not required by the Food and Drug Administration (FDA) for movement of products into Phase I clinical testing, but strong immunogenicity in humans and proof-of-concept protection in NHPs will undoubtedly be a driving force to move products beyond Phase I trials in human testing. Thus, access to NHPs for comparative study and testing in appropriate models is essential as early as possible in vaccine testing so that these studies can be integrated with decisionmaking for human trials. To enable comparative immunology studies, the NIH should support the production and distribution of standardized, quality-controlled panels of virus isolates and/or viral pseudotypes for assays. These should be made available to HIV vaccine investigators to improve the ability to compare and optimize vaccine candidates. Access to central laboratory resources for comparison between advancing HIV vaccine candidates should be a top priority to assist facilitated movement and selection of promising approaches in clinical studies.

PRIORITY FOR FUTURE RESEARCH:

- **Improve the linkage of vaccine design efforts with the clinical trial networks and cohorts/populations being identified for clinical trials to better integrate preclinical data into human vaccine trial planning and to inform and educate all stakeholders. Conduct appropriate preparative work in trial sites, particularly in international sites and racial and ethnic minority communities, to provide critical viral and immunological information to inform vaccine trial design while helping to develop strong, sustainable research infrastructure and advocacy for HIV vaccines.**

Through the HVTN and other mechanisms, the NIH, in coordination with other agencies (through PAVE) and alliances that are being formed (GHAVE), plans to support sufficient pretrial infrastructure to assess epidemiological issues such as incidence and immune responses to regionally and temporally acquired HIV isolates. Additional studies in natural history for information about viral load endpoints, normal values for clinical biomarkers, background vector immunity in the population, coinfections, behavioral risk, and other relevant health factors will enable training in laboratory experimentation and data analysis, and will lead to the development of a cadre of site investigators with experience in vaccine-related biomedical research. Further linkage of vaccine basic research and newly developing scientific and clinical infrastructure at sites as quickly as possible is desirable so that basic research questions related to HIV epidemiology and transmission, as well as vaccine design and development, are addressed and the sites involved can engage in training for a broader, more sustainable research infrastructure.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE - A:

Increase scientific knowledge through basic research on protective immune responses and host defenses against HIV to facilitate the development of vaccines and other biomedical intervention strategies to prevent and/or control HIV infection.

STRATEGIES:

- Define the mechanisms underlying protective systemic and mucosal immunity to HIV and other closely related lentiviruses by pursuing research in models that will provide information directly relevant to HIV infections; this includes the following areas of interest:
  - Determine the mechanisms of immunologically mediated control of infection with HIV and other related lentiviruses, including the role of antigen-specific (adaptive) and antigen-nonspecific (innate) cellular and humoral immunity in inhibiting viral replication to provide a basis for optimal vaccine design.
  - Define the structure-function relationships and the antigenicity and immunogenicity of HIV envelope proteins, including transient or intermediate and conformational domains induced by virus interacting with CD4, chemokine, dendritic cell (DC) surface proteins and adhesion molecules, and other cellular receptors to improve vaccine designs to more effectively induce immune responses to block infection by active T-cell immunity and protective antibody.
  - Define and characterize viral B-cell and T-cell epitopes that induce protective immunity in HIV or AIDS-related disease; utilize structural analysis of envelope to determine whether and how their immunogenicity can be improved and exploited in vaccine development.
    - Determine the mechanism of how HIV and closely related lentiviruses evade or escape from humoral and cellular immune responses; design vaccine approaches to prevent this; and define conserved epitopes in which genetic substitutions cannot be tolerated by the virus.
    - Characterize pathways of antigen processing of HIV proteins, including envelope glycoproteins, for presentation by major histocompatibility complex (MHC) class I and class II molecules. Investigate the interaction of HIV proteins with antigen-processing mechanisms that enhance or inhibit specific epitope presentation to the immune system.

- Study the role of DCs in the induction of immunological memory and long-term protective function of different subsets of human lymphocytes in HIV-related disease and in response to vaccination.
- Define factors that favor establishment and maintenance of memory cells able to generate effective recall to vaccine antigens, particularly HIV and viral antigens of closely related lentiviruses, and development of long-term protective immunity, particularly in human subjects.
- Study the mechanism of action of vaccine adjuvants for HIV immunogens that enhance HIV/SIV antigen presentation to induce different cytokine or chemokine responses, innate immunity, and host factors; carry out comparative translational research in NHP and human vaccines.
- Determine how chronic infection with one strain of HIV or closely related lentivirus, including attenuated viruses, confers protection against subsequent infection or reduces viral replication of a second pathogenic virus strain. Define the properties of the virus and of the immune responses that are responsible for lack of disease induction by attenuated viruses and/or protection from challenge with related pathogenic virus, and determine the protective mechanism, duration, and extent of cross-protection.
- Define the heterogeneity of specific responses to vaccine immunogens, specifically those derived from HIV, SIV, and SHIV, within diverse tissue compartments, and identify factors that confer protection from infection by various routes including vaginal, rectal, oral, and parenteral exposure.
- Determine which factors promote development of particular human anti-HIV effector cell types, promote production of antiviral substances including chemokines, or enhance non-antigen-specific innate protective mechanisms.
- Define the basis for adaptive, antigen-specific immune reactivity (humoral, cellular, and other) across divergent HIV types (clades and biological phenotypes or immunotypes); study clinical samples from human volunteers participating in HIV vaccine trials to determine the extent of cross-reactive immune responses that can be achieved with different candidate vaccines.
- Determine whether HIV immune responses that can contribute to immune enhancement of viral replication *in vitro* can interfere with induction or propagation of vaccine-induced effector responses *in vivo*.

- Seek new clues for correlates of immune protection and vaccine design by studying HIV-infected or highly exposed but seronegative individuals, across the lifespan, and SIV or SHIV NHP lentivirus models by conducting the following research:

  - Study acutely HIV-infected individuals, exposed/seronegative, or possibly transiently infected humans (including uninfected children born to HIV-infected mothers, individuals with controlled therapy interruptions, HIV-infected individuals vaccinated with therapeutic vaccines while on antiviral therapy, and nonprogressors) to define immune responses to HIV-1 and HIV-2, potential vaccine-inducible host immune responses, and viral factors (or viral attenuations) that reduce the amounts of circulating virus and influence disease course.

  - Elucidate the functional mechanisms for protective immunity against HIV, SIV, and SHIV, including identification of specific responses by passive transfer of antibody or immune cells and deletion of selected immune subsets in NHP models.

  - Investigate the sequence of events required for mucosal transmission/infection of HIV, SIV, or SHIV at different portals of entry to define how and where specific immune effector mechanisms can impede viral entry and/or prevent establishment of infection.

    Study mucosal immunity to HIV and SIV antigens and other infectious pathogens being used as HIV vaccine vectors in relevant animal models and humans to develop optimal vaccine strategies for HIV antigen delivery and effective immune-based prevention of HIV transmission.

  - Acquire clinical specimens from populations relevant to HIV vaccine trials for laboratory studies; explore the molecular epidemiology, humoral, and cell-mediated immune responses to HIV-1 and their relationship to class I and class II MHC alleles; and define constraints on HIV evolution under immune selection pressure so as to guide vaccine development. Acquire appropriate, linked, epidemiological information to optimize interpretation of these analyses.

  - Monitor the effects on immune activation with intercurrent sexually transmitted diseases (STDs), malaria, tuberculosis (TB), hepatitis B and C, human papillomavirus (HPV), and other infectious diseases, and with administration of drugs of abuse or effects of ART on HIV shedding in vaccinated subjects. Model these confounding elements in NHP.

- Develop *in vitro* experimental approaches for analysis of HIV vaccine responses that will combine sensitivity, specificity, high throughput, and the ability to use small sample volumes; develop *in vitro* and *in vivo* tools to study systemic and mucosal immune mechanisms of control of virus for analysis of vaccinated individuals (across lifespan) and animals protected against SIV or SHIV by undertaking the following research activities:

  - Develop and improve NHP animal models of lentivirus infection that are practical and representative of the spectrum of HIV infections and development of AIDS, including use of appropriate HIV cellular receptors and different modes of transmission; develop genetically defined and histocompatible NHP models to facilitate immune cell transfer studies; in general, make models amenable to use in evaluating protection by vaccines and other biomedical interventions. This may be approached, in part, by a genetic sequencing, particularly of selected regions of the macaque genome.

  - Develop improved methodologies and assays to measure HIV neutralization; explore the mechanisms of virus neutralization and the reason(s) for the relative difficulty to neutralize primary HIV isolates.

  - Develop and standardize immunological reagents for HIV vaccine trials; standardize cell, fluid, and tissue processing to ensure viability and maintenance of functional capacity of cells and stability of factors in serum, plasma, and culture supernatants; and develop quality control procedures for collecting, processing, freezing, storage, recovery, viability, shipping, and tracking of samples that will be essential in large-scale HIV vaccine trials.

  - Study the function of HIV/SIV-specific CD4 T cells, CD8 T cells, and viral suppressive immune responses; develop and adapt high-throughput assays with specificity for primary HIV isolates; and make available those reagents required for HIV vaccine-related studies.

  - Develop or improve sensitive quantitative measures of HIV (and SIV) in body fluids and low-level tissue reservoirs, including genital secretions and breast milk, to assess the effectiveness of vaccines designed to lower viral load and interrupt transmission or prevent disease progression.

OBJECTIVE - B:

Design HIV antigens, adjuvants, immunomodulators, and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates by applying findings from basic, epidemiologic, and clinical research; facilitate development and preclinical evaluation of vaccine strategies in laboratory studies and animal models; and foster early and continued collaboration between academicians, other Government agencies, nongovernmental organizations (NGOs), and industry in the research and development of candidate vaccines to test a broad array of vaccine concepts and combinations of different approaches for development of potential HIV vaccine products, including vaccines for particular populations.

STRATEGIES:

- Multiple parallel approaches to development and testing of candidate HIV/AIDS vaccines will be investigated to provide complementary and comparative preclinical data on safety and immunogenicity questions about HIV vaccines. Such studies should achieve the following:
  - Support the design, development, production, and testing of novel HIV/AIDS vaccine candidates for safety and for their ability to elicit appropriate antiviral immune responses. This may include, but is not limited to:
    - Virus-like particles containing one or more virus proteins, peptides, or antigens;
    - Whole-inactivated HIV rendered noninfectious by chemical and/or genetically engineered deletions of pathogenic viral elements;
    - Naturally occurring and genetically engineered, live-attenuated strains of HIV;
    - DNA or RNA coding for viral proteins;
    - Live, recombinant viral and bacterial vectors engineered to express one or more HIV proteins with attention to vectors that might provide dual benefit for HIV and some other pathogen or to vaccine vectors that target mucosal immune responses;
    - Viral replicons or other strategies to target DCs;
    - Recombinant HIV envelope protein subunits produced by a variety of methods, with an emphasis on retention or exposure (e.g., through deglycosylation) of critical nonlinear or conformational structural epitopes for induction of effective antibody responses;

        - Structurally constrained HIV envelope fragments, peptides, mimetopes, or complex peptides capable of inducing and boosting cellular or humoral immunity to HIV; and
        - Cell surface components carried on the viral surface.
- Foster collaboration between academic investigators, industry sponsors, the NIH, the FDA, other Government agencies, and NGOs on research and development of novel vaccine design concepts. These collaborations should:
    - Enable production of pilot lots of HIV vaccine candidates for testing in NHPs and human subjects;
    - Develop programs to design and conduct comparative testing of vaccine approaches with industry and academic partners that will permit long-term followup to assess disease progression in animal models; and
    - Develop infrastructure; address scientific, legal, ethical, and regulatory issues to foster and encourage participation by, and collaboration among, academic investigators, industry, affected communities and populations, and other agencies in the research, development, production, and clinical testing of candidate vaccines.
- Foster the development of HIV vaccines to optimize characteristics appropriate for broad international use, including designs exhibiting low cost with ease of production, stability, and ease of administration. This may include:
    - Combined use of two or more vaccine strategies with mixed modalities to boost the same component and/or to engage different arms of the immune response; and
    - Multivalent vaccine candidates incorporating different genetic clades and/or antigenic types to increase the breadth of immune responses.
- Support HIV vaccine design and development, incorporating methods to improve or modulate vaccine-elicited immune responses (qualitatively or quantitatively), including:
    - Novel adjuvants and delivery methods that might enhance effective DC presentation of HIV/SIV antigens;
    - Agents that stimulate or modulate mucosal immune responses to HIV or other host defenses, including cytokines or chemokines;
    - HIV/SIV vaccines formulated with cytokines or incorporating cytokine genes or other biologically active molecules in vectors; and

- Other novel strategies, including nutritional supplementation and treatment of underlying infections and/or diseases that might have an impact on HIV vaccine responses.

- Evaluate the efficacy of HIV/SIV vaccine and other immune prevention strategies in NHP animal models of HIV and closely related lentiviruses by:
  - Testing HIV/SIV vaccine and other biomedical prevention strategies in animal models that most closely mimic HIV infection in humans;
  - Determining *in vitro* correlates of an *in vivo* protective immune response generated by HIV/SIV vaccines;
  - Determining the effect of HIV/SIV vaccine formulation, site of delivery, and regimen, as well as the nature, timing, phenotype, and route of infectious SIV or SHIV challenge on the effectiveness of the vaccine-induced immunity;
  - Defining the impact of different HIV/SIV vaccine approaches on the kinetics of immune responses, kinetics and localization of viral replication, including long-term followup of disease progression in the presence of low-level chronic infection and concomitant diseases (e.g., TB, hepatitis, or autoimmune diseases), and biologic characteristics of breakthrough virus including transmissibility;
  - Determining the impact of genetic factors and age on HIV/SIV vaccine responses and on protection against virus at various challenge sites; and
  - Studying the efficacy of the HIV/SIV immune response in the face of viral mutation and variation.

- Investigate HIV/SIV vaccines and other biomedical prevention strategies with attention to potential factors such as integrity of the mucosal surface, changes in vaginal/cervical epithelium during puberty, hormonal changes during pregnancy, use of contraceptives or hormone replacement therapy, and presence of STDs; wherever possible, study potential concomitant effects on the genital tract immune responses and how inflammatory activity might compromise integrity of the mucosal surface or the inductive ability of HIV vaccines.

- Support development of reagents and standardized methods to assess specific HIV or SIV vaccine-induced immune responses in NHP animal models and humans, including infants, for both humoral and cellular aspects of systemic and mucosal immunity. This includes:
  - Developing and refining assays to distinguish between serological and cellular responses due to immunization versus those due to HIV, SIV, or SHIV infection;

- Characterizing and evaluating potential negative side effects of candidate HIV/SIV vaccine designs, including the potential to increase the susceptibility to infection or the rate of disease progression in NHP animal models;
- Standardizing and validating assays to assess potency of candidate HIV vaccines;
- Standardizing and validating assays to be used as Phase III study endpoints; and
- Abiding by Good Laboratory Practice (GLP) regulations to perform endpoint assays in support of product licensure and instituting quality assurance programs to assure sponsors and vaccine manufacturers that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with regulations stated in 21 CFR Part 58 and Part 11.

• Foster research on the safety and regulatory considerations of candidate HIV/AIDS vaccines in development:

- Whose production utilizes human-derived tumor cell and other continuous cell lines;
- That utilize vectors that have the potential to integrate into the host chromosome or have the potential for chronic expression;
- That might have the ability to be generated as either replicating or nonreplicating vectors;
- That have the potential to cause autoimmunity or highly immunogenic antivector responses; or
- That overexpress potentially harmful vector proteins.

OBJECTIVE - C:

Identify mechanisms of protective immunity to HIV in newborns and infants, and support the development of distinct study designs for safe and effective vaccine strategies and passive immune interventions, alone or in combination with other interventions, for preventing or controlling HIV infection in this population worldwide.

STRATEGIES:

- Investigate the unique immune status and develop immune interventions in both pregnant women and infants to interrupt HIV transmission. Active and passive HIV vaccine strategies need to be modeled and evaluated, particularly in infants, in parallel to studies in uninfected adults. To accomplish this goal, it is important to develop research that will achieve the following:
  - Develop relevant NHP animal models of maternal-fetal and maternal-infant perinatal transmission of HIV/SIV/SHIV that can:
    - Determine preclinical safety and immunogenicity of various HIV vaccines and adjuvants, particularly in pregnant and newborn primates;
    - Determine safety of various monoclonal and polyclonal antibody preparations against HIV;
    - Determine the best immunization routes or protocols to induce antibodies to HIV in milk and other secretions;
    - Evaluate efficacy of vaccines and passive immunotherapy for prevention of perinatal or breastfeeding HIV transmission; determine whether there is attenuation of disease progression among neonatal animals that become infected despite immune intervention; determine correlates of protective immunity; and
    - Evaluate the effect of ART in combination with immune and behavioral prevention strategies.
  - Determine virologic and nonimmunologic/genetic host factors that influence transmission of HIV-1 from mother to infant that would have an impact on selection of viral antigens for the design of an HIV vaccine or for identifying the target of immune-based intervention to prevent perinatal transmission. This includes:
    - Determining the importance of viral load and viral phenotypes and genotypes in perinatal or early infant HIV transmission and what additional viral factors are associated with differences in perinatal transmissibility;

        - Developing standardized methods to collect specimens and to detect, characterize, and quantify HIV in cervicovaginal secretions and in breast milk to determine their potential relevance in MTCT; and
        - Determining if HIV in maternal genital secretions or breast milk is distinguishable from virus found in blood and which type is transmitted from mother to fetus and mother to infant.
    - Identify maternal and infant immune responses that might control HIV replication in either the mother and/or the infant and prevent transmission of HIV or establishment of infection in infants.

- Define immune approaches that will provide specific and sustained protection against HIV/SIV transmission; develop the products necessary to achieve these goals; and develop the capacity to evaluate their safety in human subjects. This research includes the following activities:
    - Determine specific immune strategies for perinatal intervention that blocks interaction of HIV/SIV with its receptors and coreceptors and/or that targets infected cells.
    - Characterize the transmitted viral strains and monitor changes that may occur in proposed HIV vaccine trial sites; evaluate the impact that genetic polymorphism in different racial or ethnic backgrounds might have on receptor usage or immune responsiveness.
    - Evaluate, in Phase I and Phase II studies, the safety and immunogenicity of various HIV vaccines, adjuvants, vaccine administration regimens, and the pharmacokinetics of passive antibody preparations among both HIV-infected pregnant women and newborns exposed to HIV (born to HIV-infected women).
- Test the safety and efficacy of active and passive HIV vaccine interventions alone or in combination with other modes of intervention, particularly in international settings with high seroprevalence. This testing includes the following activities:
    - Identify and characterize the important issues to consider in the development of criteria for advancement of candidate HIV vaccines, adjuvants, and passive antibody preparations from Phase I and Phase II to Phase III clinical trials in pregnant HIV-infected women and/or HIV-exposed children. These criteria may include evidence of therapeutic effectiveness in mothers in addition to prevention of infection in HIV-exposed children.
    - Develop the capacity in domestic and foreign trial sites necessary to enroll mothers and infants in trials of both preventive and therapeutic

HIV vaccines, passive immunity, and other perinatal interventions with prospective long-term followup. For vaccines, this should include the assessment both of duration and breadth of detectable humoral immune responses and of memory or recall responses in the cellular immunity compartment(s).

- Conduct Phase III clinical trials for evaluation of efficacy of the most promising candidate HIV vaccines and/or passive antibody preparations that meet established criteria in pregnant HIV-infected women and/or children exposed to HIV.
- Develop criteria to define infant HIV infection status as a perinatal intervention trial endpoint in countries where breastfeeding is recommended despite maternal infection status, including type of diagnostic tests, timing of the tests, length of followup, and adherence to followup visits.
- Study HIV isolates and the immune response in infants who become infected despite administration of active and/or passive immunization to evaluate the effects of immune intervention on the characteristics of transmitted (escape) virus and on the quality, quantity, and timing of the infected infant's antiviral responses.
- Study the impact of early ART interventions and HIV vaccines given while on effective ART, on the maintenance or regeneration of antiviral immune responses in HIV-infected infants.

OBJECTIVE - D:

Conduct Phase I, Phase II, and Phase III trials for safety, immunogenicity, and efficacy with suitable candidate HIV vaccines or concepts in domestic and international settings.

STRATEGIES:

- Support the conduct of Phase I, II, and III HIV vaccine clinical trials that will determine long-term and short-term safety, evaluate efficacy, and compare immunologic responses to different preventive vaccine candidates by evaluating a broad range of humoral, cell-mediated, and mucosal immune parameters. This includes the following:
  - Design and conduct Phase I and Phase II trials using promising HIV vaccine candidates. Trials should determine safety, test immunogenicity of vaccine concepts, and address questions about optimal vaccine strain selection (i.e., the properties of a strain [immunologic, genotypic, or phenotypic]) that make it optimal for use in a selected population. Trials also should include an appropriate representation of the general populations (gender, age, ethnic and racial minority) and populations affected by HIV, and be of an appropriate size to provide data on the frequency, magnitude, and breadth of immune responses to facilitate decisions regarding initiation and evaluation of larger proof-of-concept or efficacy trials.
- Develop a comprehensive plan for conducting HIV vaccine trials with a high level of retention and adequate followup of vaccinees to reach predefined endpoints, as follows:
  - Prepare for adequate long-term followup of volunteers in HIV vaccine clinical trials to determine the durability of immune responses and protection, the correlates of immune protection, long-term safety, behavioral factors to influence adherence of followup visits, the impact of participation on risk-taking behavior, and vaccine-related reduction (or enhancement) of disease progression and HIV transmission.
  - Conduct collaborative large-scale efficacy trials of preventive HIV vaccine candidates that have proven promising, safe, and immunogenic in Phase II trials and that meet appropriate criteria by:
    - Evaluating HIV vaccine candidate efficacy against HIV infection, disease progression, and/or transmission;
    - Evaluating additional virologic, immunologic, and behavioral outcomes, particularly potential correlates of protective immunity against HIV;

- Ensuring that HIV vaccine trials are conducted with the highest regard for social, legal, and ethical standards and in populations that reflect the racial and ethnic burden of the HIV disease;
- Ensuring access to achievable, sustainable, and culturally appropriate best practices to prevent HIV exposure; and
- Developing, adapting/modifying, and coordinating educational and information programs about HIV and HIV vaccines suitable for the individual participants and communities of different ethnic, racial, and cultural backgrounds that will be involved in trials.

- Characterize the clinical course, immune responses, and other characteristics of vaccinees (e.g., behavioral risk of infection) who become HIV-infected; isolate and characterize viral isolates from participants in vaccine trials with intercurrent HIV infections to explore the possible effects of vaccination on the characteristics of escape (transmitted) viruses.
- Continue to use existing strategies to avert social harm and develop additional strategies to complement existing mechanisms at the local and national levels to reduce the risk of social and economic harm to volunteers in Phase I, II, and III HIV vaccine trials and assist in providing solutions.
- Conduct behavioral risk assessment research during HIV vaccine trials, particularly with Phase II and Phase III trial participants, to identify and evaluate any changes in risk behavior as a result of participation in an HIV vaccine trial; develop, test, and ensure access to interventions to prevent high-risk behaviors; conduct behavioral research with specific emphasis on individuals who become infected during trials to identify interventions that may prevent high-risk behaviors in future trials or application of HIV vaccines.
- Closely coordinate the evaluation of research findings on prophylactic HIV/AIDS vaccines with preclinical vaccine research and HIV immunotherapeutic interventions.

OBJECTIVE - E:

Develop strategies, infrastructure, and collaborations with researchers, communities, other U.S. Government agencies, other Governments, international and domestic NGOs, and industry that are necessary to ensure adequate performance of HIV vaccine trials, while balancing the prevention needs of the at-risk populations; identify domestic and foreign populations; and perform necessary research to define seroincidence and viral subtypes and to determine and optimize feasibility of vaccine studies in appropriate cohorts.

STRATEGIES:

- Identify and develop potential domestic and foreign sites with a high HIV seroincidence and improve access to populations at high risk for acquiring HIV infection, where vaccine or other prevention research activities may be feasible. This includes the following activities:
  - Track the course of the epidemic by applying newer epidemiologic tools for estimating the HIV incidence in various populations with documented high-risk behaviors in the United States and worldwide; improve methods to identify and evaluate emerging risk groups and those groups most likely to be informed, willing, and able participants in HIV vaccine trials.
  - Identify and address barriers to participation in clinical trials among all at-risk groups, so that all relevant populations, especially women and adolescents, are included in HIV vaccine trials.
  - Develop new laboratory diagnostic tools that can be adapted for high throughput to study new HIV infections and allow distinction between vaccinees and infected individuals.
  - Analyze MHC genetic differences and other relevant genetic or medical factors of populations at potential trial sites that might affect the qualitative or quantitative levels of immune responses to candidate HIV vaccines, susceptibility to infection, control of viral load, and disease progression.
  - Acquire and analyze HIV isolates from mucosal sites, as well as blood from recently infected people representative of potential efficacy trial populations, so that genetic and antigenic information about viruses being transmitted in the population can be obtained.
  - Develop and maintain the necessary immunology and virology laboratory infrastructure for conducting domestic and international HIV vaccine efficacy trials. This includes education and training of personnel from international sites hosting vaccine trials; development of laboratory infrastructure; standardization of assays and development of panels

of geographic-specific reagents composed of local, indigenous HIV+ and HIV- samples as well as peptide reagents to serve as controls when validating and standardizing assays that will be used in support of clinical trials in that region; and participation of trained personnel in studies related to the trial.

- Establish, build, and nurture linkages with communities and community organizations where vaccine trials might be conducted to optimize education, recruitment, and followup activities; listen to and address community concerns and social issues, and ensure ethical conduct of HIV/AIDS vaccine efficacy trials. This includes the following:

  - For all HIV vaccine trials, enlist participation of local representatives or community advisory boards (CABs) in the development of appropriate trial protocols as well as responsive mechanisms to inform and educate the participating individuals; establish networks within the community that will effectively, and on a continuing basis, address the social and medical concerns of the participants; establish mechanisms to provide ongoing information and open discussions concerning the scientific rationale and public health need for the study.

  - Develop mechanisms through CABs to engage collaboration and to provide education and the means to inform communities about HIV vaccines on a continuing basis so that social as well as medical concerns are addressed; work to establish trust in the community through open discussions of scientific rationale, expectations, and concerns.

  - For international trials, in addition, work closely with national (host) governmental and regulatory authorities, collaborating institutions or agencies, local community representatives, vaccine manufacturer(s), and the World Health Organization (WHO)/Joint United Nations Programme on HIV/AIDS (UNAIDS) to prepare for, plan, and conduct HIV vaccine trials adhering to the highest ethical and scientific standards.

- In collaboration with Government agencies, institutions, NGOs, and communities being identified as potential collaborators, explore behavioral and social issues and prevention activities that might have a substantial impact on either the design or the conduct of an HIV vaccine trial. This includes the following research:

  - Evaluate other biomedical and behavioral interventions that could prove of benefit in decreasing the incidence of HIV infection in the populations identified for future vaccine efficacy trials; address their potential impact on the evaluation of HIV vaccine efficacy.

- Conduct behavioral research in populations at high risk for HIV infection to determine, for example, appropriate risk-reduction interventions and to estimate risk behavior and recruitment, adherence, unblinding, and retention strategies pertinent to the design and execution of a successful vaccine efficacy trial, especially for populations that have been historically underrepresented in clinical trials and where the HIV epidemic is expanding disproportionately.
- Identify and develop strategies to involve the populations with highest risk for HIV transmission in different communities; particular attention should be given to adolescents and young persons who are engaging in high-risk behaviors.
- Develop research that anticipates and addresses effectively the potential adverse or unintentional effects of biomedical advances in HIV prevention (e.g., vaccines, microbicides, rapid testing, etc.), including behavioral disinhibition or increases in risk behavior such as failure to use condoms in sexual encounters, which may offset gains in prevention.
- Collaborate with other U.S. Department of Health and Human Services (DHHS) agencies and community-based organizations to develop education programs to facilitate the conduct of Phase III HIV vaccine trials in hard-to-reach populations in domestic sites; collaborate with the USMHRP, the Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), and other organizations to develop vaccine trial sites in international settings.
- Evaluate the impact of community-based participatory research in the acceptability of HIV vaccine trials.
- Develop appropriate communication strategies involving affected communities in the process of testing HIV vaccines and prepare for the eventual integration of preventive vaccines into comprehensive prevention and care programs in the United States and in countries where HIV vaccine trials are conducted.
- Determine possible adverse social, economic, behavioral, or legal consequences of participation in clinical trials; develop broadly applicable strategies for mitigating potential harm.
- Determine optimal methods of achieving informed consent for HIV vaccine efficacy trials.

- Explore innovative trial designs to improve efficiency of HIV vaccine efficacy studies (e.g., determine the impact of HIV vaccines on subsequent transmission from vaccinated individuals who become infected after administration of the

trial vaccine or utilizing initially concordant HIV-negative couples at high risk or discordant couples). This includes the following areas of trial design research:

- Consider the use of secondary endpoints, particularly immune correlates of protection, surrogates of disease progression and clinical outcomes, and the benefit of long-term followup.
- Consider the impact of early ART on HIV infections in complex trial designs.
- Encourage linkage between vaccine preparedness studies in high-risk populations and other research activities, including research on TB and STDs.

FY 2007 OAR Planning Group for Vaccines

FY 2007 VACCINES PLANNING GROUP

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